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10/511,693	10/14/2004	Masayuki Amagai	4439-4026	9184

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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,693	AMAGAI ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-9,12,13,15,16,26 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-9,12,13,15,16,26 and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/7/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment filed November 2, 2006 has been received and entered. Claims 1-4, 6-9, 12-13, 15-16, 26 and 34 have been amended, while claims 5, 10-11, 14, 17-25, 27-33 and 35-41 have been canceled.

Election/Restrictions

Applicant's election with traverse of the invention of group IV (claims 1-41) filed June 5, 2006 was acknowledged. The traversal was on the grounds(s) that Examiner has not set forth convincing argument that the search and examination of other groups necessarily represents an undue burden for the examiner. Applicants' argument of examining all groups with the elected group was found persuasive in part. Upon review of the claims and specification, Examiner agreed that it would not be undue burden to examine all groups together. Accordingly, the restriction requirement was withdrawn.

Claims 1-4, 6-9, 12, 13, 15-16, 26 and 34 are under consideration.

Information Disclosure Statement

The references cited on form PTO-1449 have been considered by the Examiner.

Maintained &New-Claim Rejections –Necessitated by amendments- 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-9, 12, 13, 15-16, 26 and 34 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims are drawn to a remedy to be used in gene therapy of genetic diseases comprising an immunosuppressive agent and a gene delivered in a form of naked DNA or in a liposome subsumption form. Subsequent claims limit the immunosuppressive agent to include an active ingredient that inhibits the interaction between a CD40 receptor ligand, CD40L, and a CD40 receptor on the surface of antigen presenting cells. Claim 6 limits the genetic disease to include a recessive genetic disease, subsequently limiting to an autosomal recessive genetic disease. Claims 8-9, 26and 34 are directed to a method for treating genetic disease according to remedy of claims 1-3.

It is emphasized that although claims 1-4, 6-7 12, 13 and 15-16 in part simply are products, they recite and encompass a remedy to be used for gene therapy of genetic disease. Therefore, they have been analyzed for their intended use in the treatment of plurality or genetic disorder more specifically autosomal recessive disease. This analysis is based on the fact that remedy for a disease, would only result in a positive outcome in the treatment of genetic disorder.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ 1400, 2d at 1404. Such factors are: (1) The breadth of the claims; (2) The nature of the invention; (3) The state of the art; (4) The level of one of ordinary skill in the art; (5) The level of predictability in the art; (6) The amount of direction and guidance provided by Applicant; (7) The existence of working examples; and (8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention and therefore, applicant's claims are not enabled.

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working example are not disclosed in the specification, therefore enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore, skepticism raised in enablement rejections are those raised in the art by artisan of expertise.

The aspects considered broad are: remedy to be used in gene therapy to treat any genetic disorder subsequently limiting to plurality of autosomal recessive genetic disease, any route of administration, any immunosuppressive agent subsequently limiting active ingredient an antagonist which inhibits the interaction between a CD40 receptor ligand, CD40L, any route and method of administering naked DNA or liposome.

It is noted that as instantly recited, claimed invention reads on broad genera of gene therapy by delivering composition comprising a polynucleotide for correcting a deficient gene responsible for genetic diseases into a subject is generally not enabling due to problems with, *inter alia*, targeting and expression of transgene at effective level by naked DNA or liposome to elicit therapeutic effective response. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed remedy and method in expressing any gene at any levels in any subject administered via any route for the treatment of any genetic skin disorder (emphasis added). An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of gene delivery *in vivo* by naked DNA /liposome is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced in any subject. As will be shown below, broad aspects were not enabled for the claimed invention at the time of filing of this application because neither the specification nor the art of record taught sufficient guidance to practice the claimed

invention. For purposes to be shown in the state of the prior art, the question of lack of enablement is discussed.

As a first issue, the claims 1-4, 6-9, 12, 13, 15-16, 26 and 34 are broad and embrace remedy to be used in gene therapy of any genetic skin diseases comprising an immuno-suppressive agent and delivering a naked DNA of gene responsible for genetic diseases by any route. The specification teaches that plasmid vector based gene transfer methods could be used to correct nucleic acids encoding the desmoglein (dsg) (see page 16, lines 4-15 of the specification). The specification further teaches an expression vector using CMV promoter (plasmid pcDNA: mDsg3), which is injected into Dsg3-/- mouse superficial dermis (example 1). It is noted that immuno fluorescence staining shows the expression of MDsg3 expression between epidermal cells of pcDNA: mDsg3-introduced site 18 hours after the injection of plasmid DNA (Figure 1a, example 1). However, the specification has provided no working example showing that disclosed remedy could be expressed at sustained levels by administering the naked DNA/liposome to any site by any method. Prior to instant invention, the art teaches a remedy for any genetic disorder involving plasmid DNA or liposome for correcting the deficiency of the gene was not predictable. The state of the prior art with respect to delivery of naked plasmid DNA effectively summarized by the reference of Niidome et al. (Gene Ther. 2002, 9(24): 1647-52) note: "owing to rapid degradation by nucleases in the serum and clearance by the mononuclear phagocyte system, the expression level and the area after injection of naked DNA are generally limited." (Column 1, page 1648). The authors conclude "we are far from the perfect gene carrier suitable for use. ..."we are still relatively ignorant about factors controlling the stability, pharmacokinetics and bio-distribution of non-viral vectors. Much of the above effort has been carried out in rodents and whether the new improvements are applicable to larger animals remains to be seen. We are still far from the perfect gene carrier suitable for clinical use, and much more work is still ahead of us" (paragraph 1, p. 1651). This assertion is further supported by non-uniform and poor expression of TGase1 gene after direct injection (Choate et al Hum Gene Ther. 1997;8(14): 1659-65). It is further noted that, direct injection failed to correct the central histological and functional abnormalities of the

disease suggesting that only partial restoration of gene expression can be achieved via direct injection of naked DNA in human genetic skin disease tissue (see abstract). It is evident from the cited art that the administration of plasmid DNA encoding any gene for correcting deficient gene for genetic skin disease by delivering naked DNA or liposome is not routine and remain unproven and unpredictable.

As a second issue, the scope of invention as claimed encompasses a remedy to be used in gene therapy of any genetic skin disease comprising administering any immunosuppressive agent. Subsequent claims limit the remedy to include an antagonist that inhibits the interaction between a CD40 receptor ligand, CD40L, and a CD40 receptor on the surface of antigen presenting cells. The specification contemplates plurality of immunosuppressive including Cyclosporin A, tacrolimus (FK506), Cyclophosphamide, azathioprine, mizoribine, steroid, Methotrexate, antihistamine and others such as antibody against CD40L (see page 13, para 1). The specification also teaches that naked DNA injection in Dsg3-/- mice resulted in anti-Dsg3 IgG antibody in the serum (see example 2, Figure 2). It is noted that the imunne responses against a desmoglein 3 (Dsg3) in a DSG3 knockout mouse can be prevented by blocking the co-stimulatory interaction of CD40 on APC with CD40L on CD4+ T-helper cells (example 3-5). Miller et al (Transfus Med Hemother 2005; 32:322–331 & Transplantation, 2001, 72(8), S5-S9) while reviewing the state of immune tolerance describe it to be a "multi-step process, which is also induced by a great variety of mechanisms influencing both T and B cells and their precursors. A defect in one of the many genes that control the development and function of self-reactive T or B cells can lead to a plethora of autoimmune conditions. Devising ways to influence some of these genes may possibly yield practical results. Miller further asserts" although immunological tolerance was first proven experimentally in 1953, more than half a century later we are still unable to induce effective and long lasting specific tolerance in transplantation" (see page 331). It is unclear from the specification that how B-cell tolerance correlates with T-cell tolerance as described in instnat application for the breadth of the claims. Furthermore, Reipert et al (Throm Hemost, 2001, 86, 1345-1352) while studying the role of CD40/CD40L interaction in immune tolerance conclude "that the blockade of

CD40/CD40L interactions during the treatment of hemophilic E-17 mice with human FVIII completely prevents the development of anti-FVIII antibodies and suppresses the induction of FVIII-specific T cells. The initial blockade of costimulatory interactions is, however, obviously not sufficient to induce a lasting immune tolerance against FVIII. The initial immune suppression is abolished after the omission of the blocking anti-CD40L antibody in subsequent challenges with FVIII. It is apparent that each method of immuno suppression requires further experimentation that is not routine and subject to variation in physiological results. Thus, it is clear without any specific guidance on regulation of immune system and merely relying of CD40L antagonism is not enabling, because of the art, as shown above, does not disclose how B cell would correlate with T cell and how CD40 antagonism could results in sustained immune tolerance that is required for repeated dosing of naked DNA. Artisan could not predict, in the absence of proof to the contrary, that such a method would be efficacious in maintaining sustained immune tolerance. An artisan would have to carry out extensive experimentation to make use the invention, and such experimentation would have been undue because of the art of lasting immune tolerance is unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

As a third issue claims 1-4, 6-9, 12, 13, 15-16, 26 and 34 embrace introducing a nucleic acid encoding a polypeptide via any route of administration (i.e oral, intranasal, intramuscular, intravenous, subcutaneous etc.). It has been difficult to predict the efficacy and outcome of transduced therapeutic gene because several factors govern the expression and/or therapeutic potential of transduced gene *in vivo* (emphasis added). The transduction of target cells represent the first critical step in any gene based therapy, which not only depends upon the type of target cells but also on the choice and/or characteristics of delivery vehicle. In addition, besides the limitations in gene transfer the problem to selectively target cells *in vivo* is still one of the most difficult obstacles to overcome (as discussed before, *supra*). For example, upon systemic administration the non-viral particle may bind to many cells they encounter *in vivo* and therefore would be diluted before reaching their targets. Besides direct administration into skin, the specification provides no other specifics or showing that other routes of

administration would result in expression in skin or other organs for the treatment of plurality of genetic disorder. The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in humans by administering claimed compositions via any route. An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of the gene delivery was not routine rather it was unpredictable and specification fails to provide any guidance as to how the claimed method would have been practiced.

As a final issue, the claims 1-4 and 8, embrace a remedy to be used in gene therapy of genetic skin disease and a method for treating genetic skin disease more specifically autosomal recessive genetic disease. The specification contemplates remedy for a number of disease including pemphigus, recessive genetic epidermolysis bullosa hereditaria dystrophica, junctional epidermolysis bullosa hereditaria, hemidesmosome epidermolysis bullosa hereditaria, ichthyosis congenita, albinism, Tay-Sachs disease, Wilson disease, Cystic Fibrosis, Phenylketonuria, type I glycogenosis, galactosemia. Examples of sex-linked genetic diseases include achromatopsia, hemophilia A, Duchenne type muscular dystrophy to name few. In addition, it is noted that specification teaches introducing desmoglein by injection to demonstrate transient expression of dsg at the site of injection. The specification also describes a grafting a wild type skin that expresses a normal Dsg3 protein onto a Dsg3-/- knockout lacking Dsg3. It is noted that this transplantation experiment can be considered analogous to skin gene therapy that introduces the normal Dsg3 gene into skin where normal Dsg3 expression is lacking. It is also noted that the titers of the anti-Dsg3 antibody immune response could be reduced by costimulation blockade in animals treated with antibodies that bound CD40L (example 6). However, this disclosure does not provide sufficient guidance to an artisan to treat any genetic skin disorder. The instant claims read on treating any genetic skin disorder in any subject using the claimed remedy and method. However, it is unclear which conditions are treatable by the claimed remedy and method (emphasis added). Passeron et al (Clinics in Dermatology, 23(1), 2005, pp 56-67) in a

post filing art disclose "127 loci are known to affect pigmentation in mouse when they are mutated". However, it is noted that the only one third of gene involved is presently identified (abstract). Passeron et al describe that Dyschromatosis symmetrica hereditaria is a very rare autosomal skin disorder characterized by the association of hypo pigmented and hyper pigmented macules mostly on the back of the hands and feet. In spite of some advances in understanding of this disorder, the pathogenesis leading to these characteristic pigmentary troubles is largely unknown (pp 65, col. 1, para 2, lines 17-21). Thus, states of art clearly suggest that many of genetic pigmentary disorder of different pathology and etiologies involve different and distinct mechanisms that are presently not completely elucidated. It is clear that skilled artisan would require new invention and undue experimentation to practice the remedy and method as contemplated by the instant claims particularly given the unpredictability of nucleic acid therapy as whole and unpredictability expressed in the art for the gene delivering in the treatment of genetic disorder in any subject.

The cited arts clearly indicate an unpredictable status of the gene therapy art pertaining to treatment of genetic disorder by naked DNA or liposome that require sustained expression of transgene at a specific site for prolonged period of time.

In conclusion, in view of breadth of the claims and absence of a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for the claimed inventions. The specification and prior art do not teach a method of *in vivo* delivery of gene such that it is expressed at therapeutic effective level for desired duration at any sites of any subject suffering from any skin genetic condition (emphasis added). An artisan of skill would have required undue experimentation to practice the remedy and method of gene therapy. Since gene therapy is clearly unpredictable in terms of achieving desired levels of gene expression for appropriate duration to results in a therapeutic effect in correcting any genetic skin disorder (emphasis added) at the time of filing of this application as supported by the observations in the prior art.

Response to Arguments

Applicant's arguments filed November 2, 2006 have been fully considered but they are not persuasive. Applicants in their argument state that instant specification shows that the disclosed remedy is expressed at sustained level. Applicants argue that anti-Dsg3 IgG antibody production by transferring Dsg3 gene (example 2) results in antibody production that last for up to 60 days. Applicants further assert that presence of antigen (Dsg3) in Dsg3 knockout animal is evidence that Dsg3 is being sustainably expressed in these knockout mice. Applicants conclude that instant specification shows that disclosed remedy is expressed at sustained level. In addition, applicants further assert that even if the remedy is not sustainable, the problem could be solved with repeated administration of the remedy (page 6 and 7 of the argument).

In response, Examiner agrees with the applicants assertion that instant specification teaches administration of plasmid comprising nucleic acid encoding Dsg3 resulted in anti-Dsg3 IgG as stated in previous office action. However, in the instant case, the issue is not whether administration of any therapeutic gene resulted in antibody production for sustained period, rather issue is whether administration of transgene results in uniform expression of transgene in the target cell at therapeutic appropriate levels for sustained period of time. In the instant case, applicant mostly argues sustained presence of antibody against antigen (dsg3). It is emphasized that presence of anti Dsg3 antibody for sustained period does not provide adequate guidance to an artisan that Dsg3 or any other transgene as claimed is expressed in the target cells at minimum effective level required for any therapeutic response. Prior art teaches that expression level and the area after injection of naked DNA are generally limited (supra) which is also supported by Choate et al showing non-uniform and poor expression of TGase1 gene after direct injection (Supra; Choate et al Hum Gene Ther. 1997;8(14): 1659-65). It is further noted that, direct injection failed to correct the central histological and functional abnormalities of the disease (see abstract). Therefore, antibody response to a gene could only provide evidence of presence of gene product, however, mere presence of a gene product would not be efficacious for correcting

plurality of genetic skin disorder as claimed. It is emphasized that neither specification nor prior art teaches that if plasmid comprising nucleic acid encoding a therapeutic gene is translated in enough of quantity in "target cells" to elicit any pharmacological response. It is noted that numerous factor including fate of vector, volume of distribution, rate of clearance in tissue, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of RNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced significantly differ depending on protein being produced (Ecke et al, Goodman & Gilman's The Pharmacological basis of Therapeutics, McGraw-Hill, New York, NY. pp 77-101). It is emphasized that instant specification at best provides some guidance towards how to induce and maintain tolerance to normal therapeutic proteins while delivering therapeutic gene. The breadth of the claim embrace delivering plurality of plasmid encoding therapeutic gene for the treatment of known and unknown genetic skin disorder. Thus, it is apparent an artisan would have to perform undue experimentation in order to determine if enough of transgene is expressed and made by administering remedy to be used in gene therapy of genus of genetic skin disease by administering the composition via any route.

As a second issue, Applicants cites references of Noelle et al and Foy et al to show that anti-CD40L antibody is an appropriate immunosuppressive agent to attain both T-cell and B-cell immune tolerance. Applicants arguments and evidence have been fully considered and are persuasive in part. Applicants also assert that administration of anti-CD40L antagonism into mice resulted in immune tolerance sustained for 42 days and it is possible to sustain immune tolerance with repeated administration of anti-CD40L antibody.

In response, Examiner agrees with the applicants that administration of anti CD40L antibody may be appropriate to attain both T and B cell immune tolerance and therefore rejection pertaining to this "is withdrawn". The breadth of the instant claims embrace a remedy comprising any immunosuppressive agent subsequently limiting to

any agent that may inhibit the interaction between CD40 receptor ligand, CD40L. The specification list a number of immunosuppressive including Cyclosporin A, tacrolimus (FK506), Cyclophosphamide, azathioprine, mizoribine, steroid, Methotrexate, antihistamine and others such as antibody against CD40L (see page 13, para 1, supra). The specification has exemplified the use of anti-mouse CD40L monoclonal antibody MR1 adequate for prevention an unfavorable immune reaction to delivery of the theraputic gene. Prior to instant invention, Reipert et al (Throm Hemost, 2001, 86, 1345-1352) while studying the role of CD40/CD40L interaction in immune tolerance conclude initial blockade of co stimulatory interactions is not sufficient to induce a lasting immune tolerance against gene product (supra). It is noted that most of these immunosuppressive agents such as corticosteroids or cyclosporine exert generalized immunosuppression. It is emphasized that this would not be suitable remedy for correcting a genetic skin disorder that may require multiple adminstarion of theraputic gene directly to the traget cells and a general review of prior art indicates that most of the immunosuppressive agent exert generalized immunosuppression and that may not involve complete inhibtion or blocking as examplified and argued by applicants using anti-mouse CD40L monoclonal antibody.

As a third issue, Applicants cite RadhaKrishnan et al (WO 99/59638) used in obviousness type rejection to argue that administration of naked DNA was routine at the time of filing of the instant application. Applicants cite Examiner that it will require routine experimentation to deliver gene as naked DNA/plasmid before filing of this application. Applicants also cite *Hybritech Inc. v. Monoclonal antibodies*, Inc. 802 F. 2d 1367 231 USPQ 81 for support that a " a patent need not teach and preferably omit what is well known in the art."

In response, it is emphasized that issue at hand is not whether naked DNA or plasmid could be delivered, rather issue it is difficult to predict the efficacy and outcome of transduced therapeutic gene because several factors govern the expression and/or therapeutic potential of transduced gene *in vivo* (See office action dated 8/4/2006, page 9, last para). Furthermore, in the instant case, claims have been amended to treat genetic skin disease by delivering plasmid via any route. Prior art, teaches non-uniform

and poor expression of TGase1 gene after direct injection to the skin (supra). This is further supported by McCluskie et al showing that route of delivery of DNA vaccine influences immune responses in laboratory animals (McCluskie et al 1999 Mol. Med. 5:287-300; Abstract). Specifically, in one study McCluskie et al observed lack of response to non-injected routes of administration of DNA based plasmids, such as oral routes, sub lingual, inhalation and vaginal wall due to variation in transfection efficiency (see Figure 1, page 292, col. 1, last para.). McCluskie et al also emphasize that route of adminstration of plasmid DNA influences the strength and nature of immune resposne in mice and non-human primate and the results in mice are not always predictive in higher mammals (see page 296, col. 2, para. 3). Althogh adminstration of plasmid or naked DNA is routine, however, it is difficult to predict the efficacy and outcome of transduced therapeutic gene. In the instant case, claims very broadly encopass treatment of any kind of genetic skin disease with only the general circular definition in the claim that the remedy comprises an immunosuppressive agent and a gene correcting a deficient gene. These would have required undue experimentation to make and use the invention because neither the specification nor the art of record provide adequate guidance as to how delivery of plasmid or naked DNA via any route would result in uniform expression of gene product in the target cell, particularly since plasmid delivery via different route show variable expression pattern (supra). It is noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh,* 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. *In re Goodman,* 29 USPQ2d at 2013 (Fed. Cir. 1994), citing In re Vaeck, 20 USPQ2d at 1445 (Fed. Cir. 1991). An artisan would have to perform undue experimentation to determine the optimal route of adminstreing the remedy such that transgene is expressed uniformly in traget cell at minimum effective level for desired duration for the treatment of genus of genetic skin disease as recited in the instant application.

As a fourth issue, Applicant argues that instant claims have been amended to direct the invention to genetic skin disease. Applicants agues that those skilled in the art can thereby specify the disease, which are treatable by the claimed remedy and thus the instant invention is fully enabled.

In response, it is emphasized that breadth of the claim embrace remedy and treatment of any genetic skin disease subsequently limiting to few. Prior art teaches very rare autosomal skin disorders such as Dyschromatosis symmetrica hereditaria that is characterized by the association of hypo pigmented and hyper pigmented macules mostly on the back of the hands and feet. It is noted that in spite of some advances in understanding of this disorder, the pathogenesis leading to these characteristic pigmentary troubles are largely unknown (Passeron et al pp 65, col. 1, para 2, lines 17-21). Thus, states of art clearly suggest that many of genetic pigmentary skin disorder of different pathology and etiologies involve different and distinct mechanisms that are presently not completely elucidated. Thus, it is apparent that there would also be no suitable animal model to test the efficacy of any potential remedy for these rare genetic skin disorders. An artisan would require undue experimentation to practice the remedy and method as contemplated by the instant claims particularly given the unpredictability of nucleic acid therapy as whole and unpredictability expressed in the art for the gene delivering in the treatment of genetic skin disorder. The specification has exemplified grafting a wild type skin that expresses a normal Dsg3 protein onto a Dsg3-/- knockout lacking Dsg3. The specification teaches that titers of the anti-Dsg3 antibody immune response could be reduced by costimulation blockade in animals treated with antibodies that bound CD40L (example 6). It is noted that applicants have included the limitation to include other forms of Epidermolysis Bullosa, however, in a post filing art, Capt et al (Journal of Investigative Dermatology (2005) 124, 530–535) state that "attempts to use knockout models of junctional Epidermolysis Bullosa (JEB) mice have failed because of the perinatal lethality of the mutant phenotype. Capt emphasises the importance of estabilishing a model system of immune competent JEB animals. It is noted that several years after filing of this application Capt et al characterize spontaneous animal model of JEB by determining the molecular basis of the disease and established the precise

genotype–phenotype correlation. Thus, it is apparent that the guidance provided in the instant applicantion required further experimentation to use an appropriate animal model for testing the efficacy of the plaurality of the remdey in the treatment of any genetic skin disease as embarced by instant claims.

Withdrawn-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 6-8, 26 and 34 rejected under 35 U.S.C. 102(b) as being anticipated by Radhakrishnan et al (WO 99/59638, dated 11/25/1999) is withdrawn in view of amendments to the claims that require genetic skin diseases not taught by Radhakrishnan.

Withdrawn-Claim Rejections - 35 USC § 103

Claims 1-4, 6-8,12, 13, 15-16, 26 and 34 rejected under 35 U.S.C. 103(a) as being unpatentable over Dwarki et al (WO 99/06562 dated 2/11/1999, IDS); Radhakrishnan et al (WO 99/59638, dated 11/25/1999) and Takahama et al (EP 1142473, dated 10/10/2001, IDS) is withdrawn in view of amendments to the claims.

Claims 1-4, 6-9, 12, 13, 15-16, 26 and 34 rejected under 35 U.S.C. 103(a) as being unpatentable over Dwarki (WO99/06562 dated 2/11/1999, IDS); Radhakrishnan et al (WO99/59638, dated 11/25/1999), Takahama et al (EP 1142473, dated 10/10/2001, IDS) and Chen et al (Journal of Biological Chem., 275, 32 24429-24435) is withdrawn in view of amendments to the claims.

Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh
Au 1632

Anne-Marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER